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Simple estimate of the influence of competitive inhibition on PBTK based risk assessment

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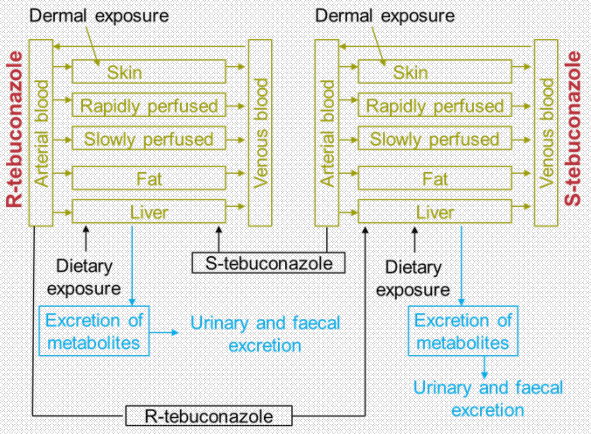
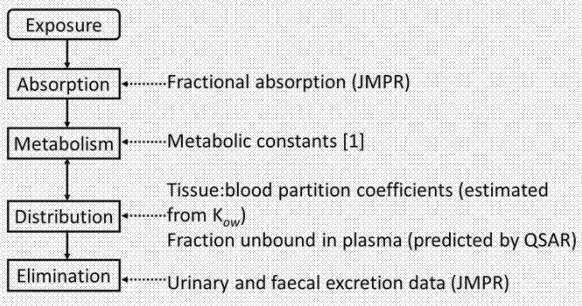
Background: In recent years, increased focus has been on the development of methods for assessing health risks caused by exposure to mixtures of chemicals from food and the environment. It has been recommended by international bodies to consider physiologically based toxicokinetic (PBTK) modelling for higher tier cumulative risk assessment of chemicals. Another important area for the use of PBTK is risk assessment of aggregate exposure via different routes (dietary, dermal, etc.).

Method: The competitive inhibition was examined in a binary PBTK model. As an example simulations for a mixture of the R- and S-enantiomers of the pesticide tebuconazole was examined.



Structure of the model.

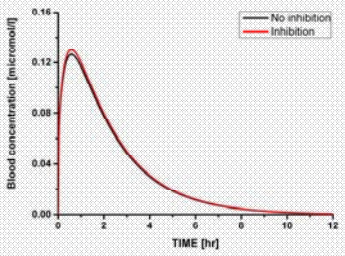


Sources for ADME data used in the development of the PBTK models. Abbreviations: JMPR: Joint FAO/WHO Meeting on Pesticide Residues. QSAR: Quantitative Structure Activity Relationship.

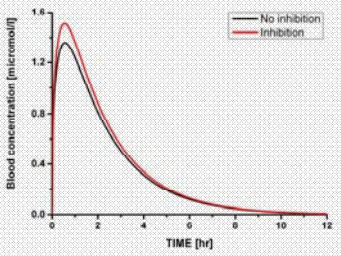
Model validation: Good agreement between experimental and simulated half-lives for R- and S-tebuconazole in rat and rabbit:

Species	Experiment, R/S tebuconazole	$T_{1/2}$ (exp.) [1, 2]	$T_{1/2}$ (pred.)
Rat	*In vitro*, with inhibition	36 min.	50 min.
Rabbit	*In vivo*, with inhibition	104 min.	111 min.

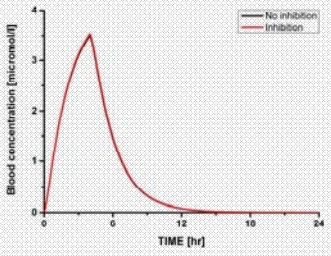
Results: Simulations made at different single oral doses in rat showed only minimal effect of inhibition at doses up to 1 mg/kg bw (0.5 mg/kg bw of each enantiomer) (graph A). Effect of inhibition was seen after a single oral dose of 10 mg/kg bw (graph B), but not after corresponding dermal exposure (graph C). Internal dose levels were affected by inhibition after 100 mg/kg bw dermal exposure (graph D).



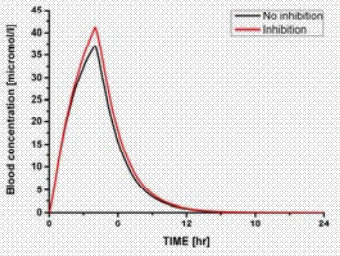
A. Concentration of tebuconazole (R + S form) in rat blood after an oral bolus dose of 1 mg/kg bw, with and without inhibition considered.



B. Concentration of tebuconazole (R + S form) in rat blood after an oral bolus dose of 10 mg/kg bw, with and without inhibition considered.



C. Concentration of tebuconazole (R + S form) in rat blood after 4 hr dermal exposure of 10 mg/kg bw, with and without inhibition considered.



D. Concentration of tebuconazole (R + S form) in rat blood after 4 hr dermal exposure of 100 mg/kg bw, with and without inhibition considered

Dietary intake for an average consumer in the Danish population and a consumer eating ≥ 550 g fruit and vegetables a day.	Estimated occupational exposure by industrial wood treatment, brushing or spraying fields (data from Danish EPA).
0.013 – 0.026 µg tebuconazole/kg bw/day [3]	4.2 – 28 µg tebuconazole/kg bw/day [4]

Conclusion: The simulations for the two binary mixtures indicate that it is not necessary to include inhibition at realistic exposure levels for humans, i.e. for exposure due to pesticide residues in food and for dermal exposure due to professional use.

Further readings:
http://www2.mst.dk/Udgiv/publications/2014/02/978-87-93178-08-3.pdf

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[4] Jónsdóttir et al., 2014. Optimization of the cumulative risk assessment of pesticides and biocides using computational techniques: Pilot project. 1-183. The Danish Environmental Protection Agency / Danish Ministry of the Environment. Bekæmpelsesmiddelforskning nr. 153.